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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/030,390	04/16/2002	Wolfgang Christian Hans	DCKQ:002	2253

7590 10/06/2004

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 10/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,390	HANS ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10,11 and 19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,11 and 19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Species Election

1) Acknowledgment is made of Applicants' election of species filed 06/17/04 in response to the election of species requirement mailed 05/28/04. Applicants have elected SEQ ID NO: 2, with traverse. Applicants argue that each sequence comprises a promoter region, trefoil peptide coding region, and secretion signal. Applicants acknowledge that each of SEQ ID NO: 1, 2 and 3 is distinct and that it is only a matter of design choice as to the selection of the promoter, trefoil-peptide coding region, and secretion signal.

Applicants' arguments have been carefully considered. Applicants' acknowledgment that SEQ ID NO: 1, 2 and 3 are distinct supports the Office's position that each sequence required a separate and non-coextensive structural search. Clearly, the Office has established the absence of sharing of significant structural elements and the existence of burdensome searches. However, since there was no art on the elected nucleotide sequence of SEQ ID NO: 2, the Office has searched all the sequences recited in the amended claim 27.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendments filed 03/01/04 in response to the final Office Action mailed 11/26/03. With this, Applicants have amended the specification.

Status of Claims

3) Claims 10, 11, 19, 20, 24, 25, 27 and 28 have been amended via the amendment filed 03/01/04.

New claim 29 has been added via the amendment 03/01/04.

Claim 28, as amended, is now rejoined with the examined claims.

Claims 10, 11 and 19-29 are pending and are under examination.

Information Disclosure Statement

4) Acknowledgment is made Applicants' Information Disclosure Statement filed 03/01/04. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Objection(s) Withdrawn

5) The objection to the drawings made in paragraph 6 of the Office Action mailed 11/26/03 is

withdrawn in light of Applicants' amendments to the drawings.

6) The objection to the specification in paragraph 8 of the Office Action mailed 11/26/03 is withdrawn in light of Applicants' amendments to the specification.

7) The objection to claims 10, 19, 20, 25 and 27 made in paragraph 15(a) of the Office Action mailed 11/26/03 is withdrawn in light of Applicants' amendments to the claims.

8) The objection to claim 27 made in paragraph 15(b) of the Office Action mailed 11/26/03 is withdrawn in light of Applicants' amendments to the claims.

Rejection(s) Withdrawn

9) The rejection of claim 10 made in paragraph 10(a) of the Office Action mailed 11/26/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

10) The rejection of claim 20 made in paragraph 10(b) of the Office Action mailed 11/26/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

11) The rejection of claim 25 made in paragraph 10(c) of the Office Action mailed 11/26/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

12) The rejection of claims 11 and 24 made in paragraph 10(d) of the Office Action mailed 11/26/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

13) The rejection of claims 11 and 19-27 made in paragraph 10(e) of the Office Action mailed 11/26/03 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claims.

Rejection(s) Maintained

14) The rejection of claims 10, 11, 19-21, 23-25 and 27 made in paragraph 12 of the Office Action mailed 11/26/03 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 - Applicants' IDS) and Malin *et al.* (*Ann. Nutr. Metabol.* 40: 137-145, 1996) in view of Steidler *et al.* (WO 97/14806 - Applicants' IDS), is maintained for reasons set forth therein and herebelow.

Applicants cite MPEP 706.02(j) and case law and state that for a claim to be obvious, there must be: (a) a suggestion or motivation to combine reference teachings; (b) a reasonable expectation of success; and (c) all of the claim limitations must be taught by the references. Applicants argue that Podolsky merely suggests as speculation that the administration of trefoil peptides could be used in the treatment of peptic ulcer diseases, inflammatory bowl diseases, and the like. Applicants mention of Podolsky's determination that trefoil peptides are naturally expressed in great abundance at the mucosal surface of the GI tract, and that their expression is greater in the proximity of the injured bowel. Applicants acknowledge Podolsky's demonstration that trefoil 'deficient' mice develop severe colonic erosions, and Podolsky's conclusion that trefoil peptides may be used to treat colonic diseases. Applicants allege that: (a) no data to support this hypothesis are advanced by Podolsky; and (b) no actual disclosure in Podolsky shows that administration of trefoil peptides *in vivo* is effective to treat lesions of the alimentary tract, specifically the colon. Applicants submit that there is no disclosure in Podolsky of *in-situ* delivery of trefoil peptides by a microorganism so as to treat gastric and/or intestinal diseases. Applicants submit that Example 3 and Figure 11 of the instant specification show that acute colitis in mice induced by DSS cannot be treated by simply administering additional trefoil peptide (mTFF1) to the site of inflammation.

With regard to Malin, Applicants acknowledge that Malin describes the effect of oral bacteriotherapy with *Lactobacillus casei* GG in the nutritional treatment of Crohn's disease and juvenile chronic arthritis. Applicants contend that Malin's use of orally administered *Lactobacillus* resulted in an increase in the guts' IgA immune response. Applicants state that Malin's conclusion is that *Lactobacillus* GG may provide a promising nutritional adjunct treatment in gastro-intestinal disorders associated with impaired mucosal barrier. Applicants allege that no suggestion is made of the use of trefoil peptides alone or in combination with *Lactobacillus* in the treatment of such gastrointestinal diseases.

With regard to Steidler, Applicants acknowledge that Steidler describes that *Lactobacteria* can be used to deliver/administer bioactive proteins *in situ*. Applicants allege that no mention or suggestion is made of using trefoil proteins and delivering trefoil proteins, or that trefoil proteins must be delivered via bacteria in order to treat diseases of the GI tract.

Applicants submit an article by Poulsen *et al.* (*Gut* 45: 516-522, 1999) which allegedly

details a study comparing oral and systemic pTEF2 with respect to the healing of gastric and duodenal ulcerations. Applicants acknowledge that some benefit was observed in Poulsen's study in the upper GI tract, but submit that no beneficial effect appeared in the colon. At page 522, lines 11-13, Poulsen allegedly states the fact that parenteral trefoil factor 2 is fermented and degraded in the caecum by bacteria and suggests that a beneficial effect of orally administered TEF2 in the colon is unlikely.

Applicants' arguments have been carefully considered, but are non-persuasive. If Podolsky disclosed the *in-situ* delivery of trefoil peptides by a microorganism to treat gastric and/or intestinal diseases, Podolsky's reference would have been used as an anticipatory prior art under 35 U.S.C. § 102. With regard to Applicants' allegation that no data is provided in Podolsky to show that administration of trefoil peptides *in vivo* is effective to treat lesions of the alimentary tract, or the colon, the following should be noted. The *prima facie* evidence for the fact that the claimed invention in Podolsky *et al* is valid and/or enabled comes from Applicants' own acknowledgment in the instant disclosure and also from other prior art references that provided similar teachings at the time of the instant invention. For example, at section (0007), the instant specification states as follows:

> (0007) The **use of trefoil proteins or peptides for treatment of disorders of and damage to the alimentary canal, including the mouth, oesophagus, stomach, and large and small intestine**, as well as for the protection and treatment of tissues that lie outside the alimentary canal **are described in WO 97/38712** and WO 92/14837. These proteins can be used either **to treat lesions** in these areas or to inhibit the formation of lesions. These lesions can be caused by radiation therapy or chemotherapy for the treatment of cancer, any other drug including alcohol which damages the alimentary canal, accidental exposure to radiation or to a caustic substance, infection, a digestive disorder including but not limited to non-ulcer dyspepsia, gastritis, peptic or duodenal ulcer, gastric cancer, MALT lymphoma, Menetier's syndrome, gastro-oesophageal reflux disease, Crohn's disease, ulcerative colitis and acute colitis of chemical, bacterial or obscure origin. Trefoil peptides are particularly useful to treat acute colitis. [Emphasis added].

Furthermore, at the top of page 3 of the instant specification, Applicants describe the teachings of another prior art reference, Babyatsky *et al.* which already disclosed the successful administration of trefoil peptide to reduce the damage in gastric ulcers and colitis. This part of the specification states the following:

> The production of trefoil peptides increases locally in regions where damage occurs such as gastric ulcers and colitis (Wright et al., 1990). **Babyatsky et al. (1996) have shown that the administration of recombinant trefoil peptides reduces the damage at those places.** In contradiction with most other proteins that are important for the protection of the mucosa (such ms epidermal growth factor), most studies have demonstrated that trefoil peptides cause little or no proliferation (Playford et al., 1996). [Emphasis added].

Babyatsky *et al.* (*Gastroenterology* 110: 489-497, 1996) is hereby made of record. As described in the instant specification, well before the publication date of Podolsky, Babyatsky *et al.* demonstrated that oral administration of exogenous recombinant trefoil peptide to rats having gastric injuries protected the rat gastric mucosa against the injuries (see abstract; Materials and Methods; and Results). Specifically under the heading 'Description of the Related Art', at section (007) of the specification, Applicants acknowledge that WO 97/38712 (i.e., Podolsky) described the use of trefoil peptides for treatment of disorders or lesions of the alimentary canal, including those of the large and small intestine, oesophagus and stomach, and lesions involved in Crohn's disease, ulcerative colitis and acute colitis. Therefore, Podolsky's disclosure is not invalid due to the alleged lack of actual disclosure.

With regard to Applicants' contention that no suggestion is made by Malin for the use of trefoil peptides alone or in combination with *Lactobacillus* in the treatment of such gastrointestinal diseases, Applicants should note that if Malin made such a disclosure, Malin would have been applied as an anticipatory art under 35 U.S.C. § 102. Malin was applied in the instant rejection to document that *Lactobacillus casei* GG was already used in the art for the same purpose, i.e., in a method of treating Crohn's disease by oral administration of a composition comprising a Gram positive bacterium, *Lactobacillus* GG, to patients with histologically confirmed Crohn's disease involving sites, such as, ileum, colon, stomach or large bowels (see Table 1; 'Patients and Methods'; and abstract of Malin). Further, it is important to note that *Lactobacillus casei* is not excluded from the scope of the claimed invention. In fact, *Lactobacillus casei* is expressly included within the scope of the invention. See the sentence bridging pages 4 and 5 of the instant specification, wherein *Lactobacillus casei* is described as a preferential non-pathogenic, non-invasive microorganism for delivering a trefoil peptide *in vivo*. Additionally, the claimed method does not exclude oral administration of *Lactobacillus casei* as a nutritional composition. Except for claim 29, the rest of the claims are not limited in scope to a method of treatment of gastrointestinal disorders (with or without involving lesions) localized in the colon.

With regard to Steidler's teachings, Applicants' acknowledgment that Steidler describes the use of *Lactobacteria* to deliver/administer bioactive proteins *in situ* has been particularly noted.

Steidler's disclosure is particularly relevant because Steidler *et al.* taught that a recombinant *Lactobacterium* can be used to deliver a range of biologically active polypeptides (see last paragraph on page 11), or any heterologous peptide or polypeptide (see page 18). Steidler *et al.* taught the broad applicability for the delivery of polypeptides via *Lactocobcteria* which are able to sustain their biological activity on a 'mucous membrane' for a sufficient length of time (see paragraph bridging pages 8 and 9). Steidler *et al.* taught that *Lactobacterium* comprises a recombinant vector comprising the polypeptide-encoding sequence under the control of a promoter sequence and a secretory signal sequence (see pages 15 and 16). Steidler *et al.* further taught that the administration of the bacterium is by nasal, oral, vaginal or anal route (see first full paragraph on page 25).

As set forth previously, given the Applicant-acknowledged therapeutic role of pS2 (TEF1) trefoil peptide in intestinal or gastric lesions, including Crohn's disease, as taught by Podolsky, and given the therapeutic effect of *Lactobacillus casei* GG also in Crohn's disease as taught by Malin *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Podolsky pS2 (TEF1) trefoil peptide recombinantly in Malin's *Lactobacillus casei* using Steidler's expression and delivery method to produce the instant invention, with a reasonable expectation of success, because Steidler *et al.* taught that any biologically active peptide or polypeptide antigen can be delivered *in vivo* via *Lactobacillus* to sustain the antigen's biological activity on a mucous membrane for a sufficient length of time. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing Podolsky's pS2 (TEF1) trefoil peptide, having a demonstrated therapeutic effect against Crohn's disease, in Malin's *Lactobacillus casei* species, which is also demonstrated to have a therapeutic effect against Crohn's disease as taught by Malin *et al.* such that a product with advantageous additive therapeutic effects against Crohn's disease can be delivered *in vivo* to the mucous membrane. The resultant invention would result in *in situ* delivery of the trefoil peptide by *Lactobacillus casei*. It was well known and obvious to one of ordinary skill in the art to combine ingredients which have been separately employed for a particular purpose in order to obtain the expected combination of benefits. See *In re Greenfield*, 571 F2d1185, 197 USPQ 227 (CCPA 1978). One skilled in the art would be motivated to combine the two compositions to produce a third composition since each of the prior art element has been taught to be therapeutically useful for

mammalian administration in a method of treatment specifically of Crohn's disease. Combining the elements/compositions or method steps known to be useful for the same purpose to form a third composition or method, also useful for the same purpose, is considered obvious. Combining known substances in an art-known method for their expected result(s) and getting nothing more than the expected result is considered obvious. See *In re Kerkhoven* 626 F. 2d 846, 205 USPQ (CCPA 1980): "It is *prima facie* obvious to combine two compositions, each of which is taught to form a third composition that is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-277, 126 USPQ 186, 188 (1960). As this Court explained in *In re* Crockett, the idea of combining them flows logically from their having been individually taught in the prior art." The rejection stands.

Applicants' failure to treat DSS-induced acute colitis in mice by administering additional trefoil peptide (mTFF1) to the site of inflammation, as depicted in Figure 11, appears to be contrary to several reports published in the prior art at the time of invention (Playford *et al.*, 1996; and Chinery *et al.*, 1995 - see below), and thus suggest that Applicant's observation could very well have been due to one or more of several factors, including, the use of suboptimal dose of mTEF1; the animal origin of mTEF1; potential improper folding of mTEF1; or lack of prolonged or repeated administration of mTEF1 etc.

Contrary to Applicants' assertion, Poulsen *et al.* make a speculative statement that pTEF2 'most probably' is fermented in the caecum by bacteria and that a beneficial effect of orally administered TEF2 in the colon is 'unlikely'. These however are mere speculations. Even if one values Poulsen's speculative statements, these statements are specific to TEF2. It should be noted that the trefoil peptide used in the instantly claimed method is not limited to, or is not required to be, TEF2. Noteworthy in Poulsen's reference are statements that support the Office's rejection and Applicants' description at section (0007) of the instant specification:

(a) Poulsen's teaching that pTEF2 accelerated gastric ulcer healing after both oral and subcutaneous administration (see fourth paragraph of the abstract);

(b) Poulsen's teaching that both oral and parenteral administration of trefoil peptides increases the resistance of the gastric mucosa (see first paragraph of the abstract); and

(c) Poulsen's teaching that a minor part of the pTEFs did enter the colon (see last paragraph of the abstract).

In addition, the knowledge in the prior art available to skilled artisans at the time of the invention is indicative that Podolsky's method would have been expected to have a reasonable expectation of success in treating disorders or lesions of the alimentary canal, including those of the large and small intestine, oesophagus and stomach, and the lesions involved in Crohn's disease, ulcerative colitis and acute colitis. For example,

A. Playford *et al.* (*PNAS* 93: 2137-2142, March 1996) showed that transgenic mice that overexpress the human pS2 trefoil peptide have an increased resistance to intestinal damage. From this, one of skill in the art would understand that adding exogenous trefoil peptide to the one produced endogenously would increase the resistance to intestinal damage. Playford *et al.* concluded that trefoil peptides are important in stimulating gastrointestinal repair (see abstract).

B. Chinery *et al.* (*Clin. Sci.* 88: 401-403, 1995) specifically taught that intestinal trefoil peptides could provide a more potent safer approach to the treatment of human gastrointestinal ulceration (see abstract).

C. Podolsky (W) 97/38712) taught that trefoil polypeptides are not degraded within the digestive tract (see last two lines on page 37).

In sum, one cannot show non-obviousness by attacking references individually where the rejections are based on combination(s) of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the claimed method is obvious over the prior-art method, given the teaching of the applied prior art. As explained above, the invention as a whole, would have been *prima facie* obvious to a practitioner in view of the knowledge in the art at the time of invention, the state of the art at the time of the invention, and the combined teachings of Podolsky, Malin *et al.*, and Steidler *et al.* Applicants have provided no evidence within the instant specification to demonstrate that the claimed method differs in any unexpected or unobvious manner from that which one of ordinary skill in the art would have expected to obtain upon combining the teachings of the cited references.

It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

15) The rejection of claims 10, 11, 19-25 and 27 made in paragraph 13 of the Office Action mailed 11/26/03 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712) in view of Le Page *et al.* (WO 93/17117), Wells *et al.* (*Mol. Microbiol.* 8: 1155-1162, June, 1993) (Wells *et al.*, June, 1993), and Wells *et al.* (*Appl. Environ. Microbiol.* 59: 3954-3959, November 1993) (Wells *et al.*, November, 1993), is maintained for reasons set forth therein and herebelow.

Applicants' arguments with regard to Podolsky's disclosure have been addressed above.

Applicants acknowledge Le Page's suggestion that *Lactococci* can be used to produce heterologous polypeptides, and that the biologically active polypeptides can be delivered in encapsulated form as oral or topical medicaments, or as vaccines. Applicants contend that there is no mention or suggestion of using trefoil peptides delivered via *Lactococcus* for treating gastrointestinal inflammatory diseases of the gut or the colon, and of using the *Lactobacteria* to recombinantly deliver trefoil peptides *in situ* in the gut for the successful treatment of GI inflammatory diseases.

Applicants acknowledge that the results from Wells Article 1 showed that *L. lactis* was capable of expressing substantial quantities of heterologous protein antigen, and that *L. lactis* is capable of presenting the expressed antigen to the immune system of a mouse in an immunogenic form. Applicants allege that there is no mention or suggestion in Wells Article 1 of recombinantly delivering trefoil proteins via bacteria in order to successfully treat diseases of the GI tract, especially the colon.

With regard to Wells Article 2, Applicants state that the article describes a recombinant expression system for the secretion of a heterologous protein for use with a lactococcal gene

expression system. Applicants acknowledge that the results indicate *L. lactis's* capability to secrete substantial amounts of heterologous protein. As with the other cited art, Applicants allege that there is no mention or suggestion in Wells Article 2 of recombinantly delivering trefoil proteins via bacteria in order to successfully treat diseases of the GI tract, especially the colon.

Applicants' arguments have been carefully considered, but are non-persuasive. Once again, Le Page *et al.*, Wells *et al.* (June, 1993), and Wells *et al.* (November 1993) were applied in a rejection under 35 U.S.C. § 103 as opposed to 35 U.S.C. § 102.

As set forth previously, Le Page *et al.* was applied to document that the delivery of a therapeutically significant polypeptide via *Lactobacteria* was well known in the art at the time of the invention. Le Page *et al.* demonstrated the use of a food-grade organism, *Lactococcus lactis*, for the recombinant expression and delivery of a variety of heterologous peptides, polypeptides or proteins of diverse origin. The recombinant product in biologically active form is delivered *in vivo* by parenteral, oral, rectal or topical route. La Page's *Lactococcus lactis* comprised a recombinant vector containing the coding sequence of the polypeptide or peptide desired to be expressed and delivered under the control of an inducible promoter sequence and a secretory signal sequence (see abstract; claims; page 4; and paragraph bridging pages 5 and 6). La Page's *Lactococcus lactis* expressing heterologous protein or polypeptide is used in the production of an immune response in an immunized subject (see page 1). It is taught by Le Page *et al.* that the use of a non-invasive microorganism to express a range of foreign proteins opens the way to the concurrent delivery of antigens and cytokines which might be used to drive an immune response in a desired direction (see page 2, first paragraph).

Wells *et al.* (November, 1993) taught the use of a recombinant *Lactococcus lactis* strain for expression of a heterologous protein using appropriate expression-secretion vectors which incorporate different lactococcal secretion leaders and translation initiation sequences, the *lac* promoter and a bacterial signal leader (see abstract; and page 3954). The expressed protein has prolonged stability in marked contrast to the proteolysis encountered in other Gram-positive expression systems (see page 3958). Wells *et al.* (November, 1993) taught that innocuous lactic acid bacteria could be used for the production of a number of heterologous proteins of high purity (see page 3954, left column). Wells *et al.* (November, 1993) taught the recombinant *Lactococcus*

expression system to be a model system for the expression of a substantial amount of a heterologous protein (see title; and abstract).

Wells *et al.* (June, 1993) demonstrated for the first time that a heterologous peptide antigen of medical importance could be successfully expressed in substantial quantities and in a soluble form via the expression system of a food grade bacterium, *Lactococcus lactis* and be presented to the immune system in an immunogenic form (see abstract; and page 1155). Wells *et al.* (June, 1993) taught that the resultant recombinant *Lactococcus lactis* expressing substantial quantities of the heterologous peptide successfully immunized mice against lethal challenge. Wells *et al.* (June, 1993) expressly taught the continuing need in the art to develop safer vaccines and a growing interest in using live recombinant bacteria as vaccine antigen delivery vehicles which may be taken by mouth (see page 1155, left column; and page 1157, right column). Wells *et al.* (June, 1993) taught how to preload the non-commensal bacterium, *Lactococcus lactis*, with an antigen for use as an antigen delivery vector (see page 1155, right column). The recombinant *Lactococcus lactis* contains the heterologous protein gene under the control of a suitable promoter sequence and the expression vector (see page 1155, right column; and page 1157).

Given the therapeutic role of pS2 (TEF1) trefoil peptide in intestinal or gastric lesions, including Crohn's disease, as taught by Podolsky, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to express Podolsky pS2 (TEF1) trefoil peptide recombinantly in Le Page's or Wells' (June or November, 1993) *Lactobacillus lactis* using Wells' (June or November, 1993) or La Page's expression and delivery method to produce the instant invention, with a reasonable expectation of success, because Wells *et al.* (June, 1993) taught that a heterologous peptide antigen of medical importance could be successfully expressed in substantial quantities and in a soluble form via *Lactococcus lactis* for antigen delivery via mouth, and be presented to the immune system in an immunogenic form; and Wells *et al.* (November, 1993) taught that heterologous proteins of high purity can be expressed in substantial amounts via the model recombinant *Lactococcus lactis* expression system. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of producing Podolsky's pS2 trefoil peptide, which has a demonstrated therapeutic effect against Crohn's disease, in Wells' (June or November, 1993) or La Page's *Lactobacillus lactis* such that a substantial quantity of

soluble pS2 can be delivered *in vivo* with cytokines for driving an immune response in a desired direction as taught by La Page *et al.* The instant claims 10, 11, 19-25 and 27 are *prima facie* obvious over the prior art of record. The rejection stands.

In sum, one cannot show non-obviousness by attacking references individually where the rejections are based on combination(s) of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants appear to argue that the combination of references fails because the prior art does not have anticipatory references regarding all elements of the invention. The argument is not persuasive. At issue is whether the claimed method is obvious over the prior-art method, given the teaching of the applied prior art. As explained above, the invention as a whole, would have been *prima facie* obvious to a practitioner in view of the knowledge in the art at the time of invention, the state of the art at the time of the invention, and the combined teachings of Podolsky, Le Page *et al.*, Wells *et al.* (June, 1993), and Wells *et al.* (November, 1993). Applicants have provided no evidence within the instant specification to demonstrate that the claimed method differs in any unexpected or unobvious manner from that which one of ordinary skill in the art would have expected to obtain upon combining the teachings of the cited references. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988).

16) The rejection of claim 26 made in paragraph 14 of the Office Action mailed 11/26/03 under 35 U.S.C. § 103(a) as being unpatentable over Podolsky (WO 97/38712 - Applicants' IDS) as modified by Malin *et al.* (*Ann. Nutr. Metabol.* 40: 137-145, 1996) and Steidler *et al.* (WO 97/14806 - Applicants' IDS) as applied to claim 10, and further in view of Silk (WO 8203329), is maintained for reasons set forth therein and herebelow.

Applicants' arguments with regard to Podolsky, Malin *et al.* and Steidler *et al.* have been

addressed above. Applicants contend that Silk describes glucose polymers useful for the nourishment of patients via the gastrointestinal tract. Applicants state that no suggestion is made by Silk to use a gastric catheter to deliver a therapeutic composition such as hypothesized by Podolsky and as modified by Malin and Steidler. Applicants submit that one of skill in the art would not be motivated to use Silk's gastric catheter to deliver Podolsky's proposed therapeutic composition as modified by Malin and Steidler.

Applicants' arguments have been carefully considered, but are non-persuasive. As set forth previously, Silk was applied in the rejection to document that the use of a gastric catheter as an alternative to the oral administration of a therapeutic composition, especially in patients who are incapable of feeding themselves, was routine and conventional in the art at the time of the invention. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Silk's gastric catheter to deliver Podolsky's therapeutic composition as modified by Malin *et al.* and Steidler *et al.* to produce the instant invention, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to produce the instant invention for the expected benefit of providing an alternative means of oral administration especially in those patients who are incapable of feeding themselves as taught by Silk. It should be noted that what would reasonably have been known and used by one of ordinary skill in the art need not be explicitly taught. See *In re Nilssen*, 851 F.2d 1401, 7 USPQ2d 1500 (Fed. Cir. 1988). The test of obviousness is not express suggestion of the claimed invention in any and all of the references, but rather what the references taken collectively would reasonably have suggested to those of ordinary skill in the art presumed to be familiar with them. *In re Keller*, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Obviousness does not require absolute predictability, (see *In re Lamberti*, 192 USPQ 278), but only a reasonable expectation of success (see *In re O'Farrell*, 7 USPQ 2d 1673, Fed. Cir. 1988). The rejection stands.

New Rejection(s)

Applicants are asked to note the following new rejection(s) made in this Office. The new rejection(s) is necessitated by Applicants' amendments to the claim(s).

Rejection(s) under 35 U.S.C § 112, Second Paragraph

17) Claims 25 and 28 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite

for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regards as the invention.

(a) Claim 25 is incorrect in the recitation 'is is by ... administration'.

(b) Claim 28 is vague, indefinite and confusing 'the recombinant vector comprises a nucleotide sequence'. Claim 28 depends from claim 27, which recites 'a recombinant vector comprising a trefoil-coding sequence'. It is unclear whether 'the recombinant vector comprising a nucleotide sequence' in claim 28 is the peptide-coding sequence, promoter sequence, the signal sequence, or an additional nucleotide sequence.

Remarks

18) Claims 10, 11 and 19-29 stand rejected.

19) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

20) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (703) 872-9306.

21) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system,

see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

22) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

September, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER